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EXAMINER	
AFREMOVA, VERA	
ART UNIT	**PAPER NUMBER**
1651	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/082,082	Applicant(s) TEI, MUNETETSU	
	Examiner Vera Afremova	Art Unit 1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-54* is/are pending in the application.

4a) Of the above claim(s) *37-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of the Group I (claims 1-36) in Paper No. 9 filed 7/02/2203 is acknowledged. The traversal is on the ground(s) that the cited references do no provide adequate support for conclusions with regard to patentable distinctness of several groups of inventions in the instant application and that there is no burden in searching all groups. This is not found persuasive. The cited patent JP 03-080076 [see abstract of the IDS reference AW] discloses a product with "activated" lymphocytes made by culturing lymphocytes with a chemical compound or anti-CD3 antibody at about 36-37 °C which is materially different from the presently claimed process requiring the heat treatment of lymphocytes at 38-50 °C and/or the treatment with a chemical compound of galenical extract. The antitumor effects of the lymphocyte-containing product disclosed by JP 03-080076 are clearly admitted by applicant (see specification page 1, lines 18-2). Thus, the inventions of Group I and the Groups III-V are distinct.

The cited patent US 5,891,653 discloses that the use of beneficial effects of stress protein (col. 1, lines 10-15) including heat shock proteins HSP (col. 1, lines 31-32) for the purpose of modulating or eliciting immune response (col. 1, line 14) including immune response towards viral infection (col. 1, line 16) or including cancer immunity (col. 2, line 13). The stress protein containing products in the method of use of US 5,891,653 are provided in a form of pure proteins or in a form of genetically engineered cells (col. 1, lines 10-14) and, thus, the method of the cited patent is practiced with another materially different product(s) that are distinct from the activated

lymphocytes with induced HSP as encompassed by the instant application and claims. Thus, the inventions of Group I and the Group VI are distinct.

Furthermore, as to the question of burden of search, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. Burden in examining materially different groups having materially different issues also exists. Clearly different searches and issues are involved with each group.

For these reasons, the restriction requirement is deemed proper and is adhered to. The restriction requirement is hereby made FINAL.

Claims 37-54 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction requirement in Paper No. 9 filed 7/02/2003.

Claims 1-36 are under examination in the instant office action.

Claim Objections

Claims are 22-36 are objected to because of the following informalities:

The Latin names of plants or other biological materials should be italicized. Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 1-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-18 and claim 1, in particular, are indefinite because it is uncertain what are components in the claimed composition or "medications". The claimed product is a product by process of making wherein the process of making neither indicates final product nor comprises recovering step. Thus, it is uncertain as claimed whether the claimed "medications" are activated lymphocytes comprising heat shock proteins (HSP) or whether the claimed "medications" are HSP. In the instant office action the claimed composition is interpreted as a composition comprising activated lymphocytes treated with heat to induce HSP (see specification page 10, line 27-28 and table 1 at page 11).

Claims 19-34 and claims 19-20, in particular, are indefinite because it is uncertain what are components in the claimed composition or "medications". The claimed product is a product by process of making wherein the process of making does not indicate the final product obtained and/or incorporated in the claimed composition. Thus, it is uncertain as claimed whether the claimed "medications" are activated lymphocytes treated with heat and/or with galenical extract or whether the claimed "medications" comprise two agents: 1) activated lymphocytes and 2) galenical extract (reserpine). The generic disclosure is not particularly clear as related to the presently claimed composition (page 9, lines 14-23). The exemplified disclosure demonstrates the separate administration of two agents: 1) heat treated lymphocytes and 2) reserpine (see page 11). It is also noted the claimed product indicates the use of multiple compositions or "medications", thus, adding to the confusion about the components in the presently claimed composition. In the instant office action the claimed composition or "medication(s)", drawn to the addition of "galenical extract" to lymphocytes, is given a broadest interpretation such as the use of galenical extract(s) for modulating immune response.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Kamwanja et al. [U].

Claims are drawn to a composition comprising activated lymphocytes treated with heat to induce HSP. The composition is intended to provide antitumor and/or antiviral effects. Some claims are further drawn to induction of HSP with molecular weight 60-80 or 70 kDA. Some claims are further drawn to lymphocytes treated at 38-50°C for 5 seconds to 6 hours or at 42-45 ° C for 10-60 minutes.

The reference by Kamwanja et al. [U] discloses a composition comprising activated lymphocytes treated with heat at 42 ° C for 60 minutes to induce HSP with molecular weight 70 kDA (table 3, page 441). The disclosed composition is identical to the presently claimed composition because it comprises identical components obtained by identical treatments as required by the presently claimed invention. Thus, the effects that would be produced by the composition of the cited reference under conditions as intended for the instant invention are presumed to be inherently identical to the properties/effects as intended for the presently claimed composition. Moreover, it is well established that lymphocytes or "activated" lymphocytes

modulate host immune response and, thus, provide antitumor and/or antiviral effects within the meaning of the claims. Thus, the cited patent is considered to anticipate the claimed invention.

Claims 1-21 are rejected under 35 U.S.C. 102(e) as being anticipated by US 6,261,839 [B].

Claims are drawn to a composition comprising activated lymphocytes treated with heat to induce HSP. The composition is intended to provide antitumor and/or antiviral effects. Some claims are further drawn to induction of HSP with molecular weight 60-80 kDa or 70 kDA. Some claims are further drawn to lymphocytes treated at 38-50°C for 5 seconds to 6 hours or at 42-45 °C for 10-60 minutes. Some claims are further drawn to addition of galenical extract of crude drugs to induce HSP.

US 6,261,839 [B] discloses a composition comprising activated lymphocytes such as natural killer cells (NK cells) treated with heat to induce HSP (see col. 7, lines 33-48). The cited patent demonstrates that heat treatment increase the amounts of HSP70 in the cell population of peripheral blood lymphocytes (see col. 8, lines 41-46, and table 2 at col. 14). Since the NK cells are present in the cell population of peripheral blood lymphocytes (see col. 2, lines 56-57) it is reasonably to presume that NK cells also comprise the HSP induced as result of heat treatment. The cited patent discloses the use of identical heat treatment in order to obtain a product with activated lymphocytes, for example: about 42°C for 2 hours (col. 8, line 33 or col.14, line 27) or at 38-43°C or 40-42 °C for one hour to several hours (col. 3, lines 53-56) or col. 11, lines 66). The cited patent teaches the antitumor effects of the heat-treated NK cell containing

compositions towards various tumor cells including leukemia cells K562 (col. 4, lines 30-35) as well as the antiviral effects of NK cells (col. 4, lines 40-47).

Therefore, with respect to claims 1-18 the disclosed composition is identical to the presently claimed composition because it comprises identical components having identical effects and produced by identical treatments as required by the presently claimed invention. Thus, the cited patent is considered to anticipate the claimed invention.

With respect to claims 19-21, drawn to the addition of "galenical extract of crude drug or its compounds" to induce HSP in the "medications"/composition, the disclosed composition is considered to be identical to the presently claimed invention because the cited patent teaches the addition of a "compound" increasing production of HSP70, for example: see product obtained by process as disclosed at col. 2, lines 39-47. Although the particular compound in the cited patent appears to be a synthetic product, the cited patent suggests the use of some naturally occurring analogs (col. 1, lines 8-11). However, the claimed invention is not limited to the use of a particular plant extract or "galenical extract" but it encompasses the use of some unidentified "compounds" or unidentified extracts as claimed wherein the claimed "compounds" appear to provide some immunomodulating effects as related to the induction of HSP. Thus, the cited patent, which teaches incorporation of a compound increasing production of HSP70, is considered to anticipate the claimed invention.

Claims 1-6 and 19-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Mekori et al. [V].

Claims are drawn to a composition comprising activated lymphocytes treated by heating and treated by addition of reserpine (galenical extract of *Rauwolfia serpentina*). The composition is intended to provide antitumor and/or antiviral effects. The composition is treated to induce HSP with molecular weight 60-80 or 70 kDA.

The reference by Mekori et al. [V] discloses a medication composition comprising activated lymphocytes or the reserpine treated lymphocytes (immune lymph node cells) exposed to heating to 37°C (page 1937, par. 5, section "in vitro treatment of I-LNC"). The activated reserpine treated lymphocytes disclosed by the Mekori reference are presumed to produce the same antiviral/antitumor effects at least to some degree as required for the presently claimed product obtained by process because the lymphocytes as disclosed by Mekori are activated and/or obtained by the same treatment as the claimed lymphocytes. Moreover, the lymphocytes are known to modulate and to reinforce host immune response and, thus, the cited lymphocytes are reasonably expected to possess antiviral and/or antitumor effects within the meaning of the claims.

With respect to claims 1, 4, 19, 22 and 25 the activated reserpine treated lymphocytes disclosed by Mekori are presumed to be identical to the claimed product obtained by process because the claimed invention encompasses the heat treatment of lymphocytes and the lymphocytes of the cited reference have been treated at elevated temperature 37°C which is higher than the normal room temperature 25°C.

With respect to claims 1-3, 20, 21, 23, 24, 26 and 27 the activated reserpine treated lymphocytes disclosed by Mekori are presumed to comprise at least some amounts of HSP60-80 or HSP70 as the presently claimed product obtained by process because the treatments of

lymphocytes, including both application of elevated temperature and reserpine, are the same as presently claimed and as disclosed by reference. Moreover, the claimed invention encompasses the induction of HSP rather than the expression of specific amounts of HSP.

Therefore, the reserpine treated lymphocyte containing product disclosed by Mekori is identical the presently claimed lymphocyte containing product obtained by process. Thus, the cited reference is considered to anticipate the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,261,839 [B] taken with JP 2001039875 [N], Wakabayashi et al.[X], Li et al.[W], Mekori et al. [V] and Kamwanja et al. [U].

Claims are directed to an antiviral/antitumor medication composition comprising activated lymphocytes treated by heating and by addition of a compound derived from galenical extract. Some claims are further drawn to induction of HSP with molecular weight 60-80 kDA or 70 kDA. Some claims are further drawn to lymphocytes treated at 38-50° C for 5 seconds to 6 hours or at 42-45°C for 10-60 minutes. Some claims are further drawn to the addition of compounds including reserpine, extract of *Rauwolfia serpentina*, extract of *Linderae radix*, safflower extract or extract of *Scutellariae radix* in the medication composition.

US 6,261,839 is relied upon as explained above for the disclosure of a medication composition having antiviral/antitumor effects wherein the composition comprises activated heat treated lymphocytes and a compound increasing HSP induction. Although the cited patent US 6,261,839 is silent with regard to molecular weight of the HSP in the heat-treated lymphocytes, the cited reference by Kamwanja et al. [U] demonstrates that the heat treatment within the claimed temperature ranges and time intervals induces HSP60-80 or HSP70 (table 2).

The cited patent US 6,261,839 teaches the use of a synthetic compound and but it is lacking particular disclosure related to the use of a specific galenical extract including reserpine or extract of *Rauwolfia serpentina*, extract of *Linderae radix*, safflower extract and extract of *Scutellariae radix.*

However, the following references are relied upon for the missing disclosure.

For example: JP 2001039875 teaches (see English abstract) that the agents obtained from extracts of *Rauwolfia serpentina* and *Scutellariae radix* including reserpine as active component can increase production of HSP and they can be used as immunomodulating agents in the medication compositions. The cited patent also teaches that the plant extracts decrease the drug side effects on living body.

Further, the references by Wakabayashi et al. and by Li et al. demonstrate the safflower extract and the extract of *Linderae radix* as immunomodulating agents (see abstracts of the references).

The cited documents including the reference by Mekori et al. and by Kamwanja et al. are also relied upon to demonstrate that the medications compositions with heat treated lymphocytes and with reserpine treated lymphocytes are known in the prior art as the medications or products

effective for immunomodulating and reinforcing host immune system and, thus, effective against viral disorders or tumor related disorders of host immune system.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to substitute the immunomodulating agents of the secondary references JP 2001039875 [N], Wakabayashi et al.[X] and/or Li et al. [W] for the immunomodulating agent in the antiviral/antitumor composition with heat treated lymphocytes disclosed by US 6,261,839 with a reasonable expectation of success in providing medications with antiviral/antitumor and/or immunomodulating effects including effects related to HSP induction in treated cells. One of skill in the art would have been motivated to substitute the synthetic immunomodulating compounds for plant extracts because the plant extracts have been suggested as agents decreasing the side effects on living body as taught by JP 2001039875. One of skill in the art would have been motivated to combine lymphocytes activated by heat treatment and/or by addition of immunomodulating compounds including reserpine or other plant extracts for the expected benefits in treating and/or reinforcing immune system while avoiding side effects on living body as suggested by the cited prior art references.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (703) 308-9351. The examiner can normally be reached on 9.30 am - 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on (703) 308-4743. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Vera Afremova

AU 1652

Septembre 17, 2003

VERA AFREMOVA

PATENT EXAMINER

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